Atrial fibrillation and heart failure due to reduced versus preserved ejection fraction

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Title: **Atrial fibrillation and heart failure due to reduced versus preserved ejection fraction: A systematic review and meta-analysis of death and adverse outcomes**

Brief Title: Kotecha *et al*; Outcomes in atrial fibrillation and heart failure

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Abstract

Background: Atrial fibrillation (AF) and heart failure frequently coexist, commonly resulting in serious adverse events. With both conditions increasing in prevalence and justified concerns about treatment efficacy, it is vital to understand how the type of heart failure impacts on prognosis.

Methods: We performed a systematic review of studies examining cardiovascular outcomes in AF patients with heart failure and reduced ejection fraction (AF-HFrEF) compared to those with preserved ejection fraction (AF-HFpEF). The primary outcome was all-cause mortality, meta-analyzed using a random-effects model. Prospective registration: PROSPERO-CRD42014007305.

Results: Thirteen studies were included in the systematic review (n=54,587) with 10 suitable for meta-analysis, including retrospective/prospective cohorts and sub-group analyses of randomized trials. AF-HFrEF was present in 49% and these patients were younger, more often male and with higher NYHA class than AF-HFpEF. Oral anticoagulation use was 55% versus 50% respectively ($p<0.001$). All-cause mortality was significantly higher in AF-HFrEF; risk ratio (RR) 1.24, 95% CI 1.12-1.36, $p<0.001$ (n=45,100), with absolute death rates of 24% compared to 18% in AF-HFpEF over 2 years. There were no significant differences in incident stroke (RR 0.85, 95% CI 0.70-1.03, p=0.094; n=33,773) or heart failure hospitalization (RR 1.21, 95% CI 0.96-1.53, p=0.115; n=31,583). The risk of bias was generally low, but heterogeneity was substantial.

Conclusions: All-cause mortality is significantly higher in AF patients with HFrEF compared to HFpEF, although stroke risk and heart failure hospitalization are similar. Further studies are needed to address the prevention of adverse outcomes in all AF patients with heart failure, regardless of ejection fraction.

Abbreviations

AF	Atrial fibrillation
CI	Confidence interval
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HR	Hazard ratio
MI	Myocardial infarction
NYHA	New York Heart Association
RR	Risk ratio

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia and is associated with increased rates of mortality and serious morbidity, including stroke, worsening of heart failure, sudden death, and reduced quality of life.[1] Both the incidence and prevalence of AF are expected to double in the next 20 years.[2] Patients with AF are twice as likely to be hospitalized as matched controls, with direct medical costs estimated to be 73% higher than non-AF patients.[3] Further, AF is an independent predictor of all-cause mortality, with a two-fold adjusted increase in death.[4, 5] While most strokes in AF can be prevented by oral anticoagulation, cardiovascular deaths in AF patients are mostly related to progressive heart failure or sudden death.[6-8] In the context of those diagnosed with a heart failure syndrome, the presence of AF leads to higher rates of death and hospitalization, regardless of other risk variables or which condition comes first.[9, 10] Depending on the severity of HF, up to 50% of symptomatic patients will be diagnosed with AF, representing a large and growing unmet clinical need for healthcare improvement.[11]

Current risk stratification schemes for AF focus on preventing strokes and systemic embolism by identifying patients at risk that either require or do not require oral anticoagulation.[1, 12] Both the $CHADS_2$ and CHA_2DS_2-VASc schemes incorporate a history of heart failure as a risk marker, although based on differing definitions and detection methods. There is conflicting evidence on whether heart failure with reduced ejection fraction (HFrEF) is the major driver for adverse clinical events or if heart failure with preserved ejection fraction (HFpEF) is equally important.[13-15] With regards to prediction of mortality, analysis of the Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) trial identified heart failure as an independent predictor of all-cause mortality in AF (adjusted for ejection fraction) and the strongest predictor of cardiac death.[6] We have recently demonstrated that in

contrast to patients in sinus rhythm, those with HFrEF and concomitant AF do not benefit from beta-blocker therapy in terms of all-cause mortality, cardiovascular mortality or hospitalization.[8] This highlights the importance of analyzing outcomes specifically in AF, rather than extrapolating from patients with sinus rhythm. With the prevalence of HFpEF now equal to that of HFrEF[16], understanding the relative effects on major adverse events in patients with AF is of major clinical importance and requires further clarification. Our objectives were to systematically assess the available literature on AF patients with heart failure to determine if clinical outcomes in AF-HFpEF were similar to those in AF-HFrEF.

Methods

Eligibility criteria & search strategy

All studies examining comparative outcomes in AF-HFrEF and AF-HFpEF were evaluated, regardless of study design. All cardiovascular outcomes and all populations were considered, including sub-sets of AF patients from larger trials. We excluded studies that did not provide comparative outcomes or were not published as full-text articles. The definitions used by each individual study were accepted, including those of AF, heart failure and whether ejection fraction was preserved or not. A systematic review of MEDLINE (1950 to November 2013 and subsequently extended to August 2014), EMBASE (1980 to December 2013) and the Cochrane Library (until December 2013 and subsequently extended to August 2014) were performed without language restriction (see study selection diagram in Figure 1). We also manually searched reference lists of relevant studies, investigated registers of ongoing trials and included studies after discussion with content experts. The review was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.[17] The project was prospectively registered with the PROSPERO database of systematic reviews (CRD42014007305).[18]

Data collection and quality assessment

Two investigators (RC and DK) independently extracted and tabulated data in a standardized data-extraction form. Discrepancies and missing data were resolved by group discussion, reference to the original publication and additional independent adjudication. Unadjusted data were extracted for meta-analysis and adjusted data for systematic review. Additional unpublished data were provided from the lead authors of two studies.[8, 19] The study by Kotecha *et al* (2014) includes pooled individual patient data from 10 randomized

controlled trials of beta-blockers in patients with heart failure.[20] In another study, outcome rates were extrapolated from the 88.9% of patients with available follow-up.[21] Study quality was assessed using the Cochrane Collaboration's Risk of Bias tool and the Risk of Bias Assessment Tool for Non-randomized Studies (RoBANS), which address key criteria such as selection bias, exposure measurement, blinding, the completeness of outcome data and selectivity of reporting.[22, 23]

Primary and Secondary Outcomes

The predefined primary outcome was all-cause mortality. Secondary outcomes of interest were incident stroke, systemic embolism, myocardial infarction (MI), heart failure hospitalization and major bleeding. Meta-analysis was suitable for three outcomes; all-cause mortality, incident stroke and heart failure hospitalization.

Statistical analysis

Demographics were averaged using a weighted mean (and standard deviation) with t-tests used for between-group comparisons. Meta-analysis was pre-specified to use a random-effects model as the true effect size was likely to vary in the individual studies owing to the variety in populations assessed and different study designs. Pooled binary event data for AF-HFrEF and AF-HFpEF were compared using a risk ratio (RR) with associated 95% confidence intervals (CI) using the method of DerSimonian and Laird.[24] Sensitivity analyses for the primary outcome were performed according to a pre-defined mean anticoagulation rate of 70% and by study design (post-hoc examination of randomized subjects compared to cohort studies). The latter analysis utilized a fixed-effects model with the method of Mantel and Haenszel[25]. Three additional post-hoc analyses were performed for the primary outcome: (1) according to ejection fraction cut-off for HFpEF (<50% or ≥50%); (2) whether the

population was derived predominantly from heart failure or AF patients; and (3) a sensitivity analysis excluding the largest study. Heterogeneity was assessed using the chi-squared test and I^2 statistic, with the estimate of heterogeneity taken from the inverse-variance fixed-effects model. Publication bias was assessed using a funnel plot, Begg's test and Egger's test. A two-tailed p-value of 0.05 was considered statistically significant. Analyses were performed on Stata Version 11.2 (StataCorp LP, Texas).

Results

We identified 13 studies (see Figure 1) which included 54,587 patients with AF and heart failure from a total population studied of 179,585 (30%). The risk of bias was generally low, except for incomplete outcomes due to the selection bias of including participants with available echocardiography data (see Supplementary Table A). Study descriptors are summarized in Table 1. From the 10 studies included in the meta-analysis (n=45,100), 5 were retrospective or prospective cohorts[19, 21, 26-28] and 5 were sub-group analyses of randomized trials.[29-32] One study examined outcomes at 30 days after heart failure admission[26], however the length of follow-up in the remainder was 1.9 years (weighted-average) with a range of 1.5-3.4 years. AF-HFrEF was present in 48.5% of patients and AF-HFpEF in 51.5%. Three cohort studies did not present unadjusted data and are discussed separately from the meta-analysis.[33-35]

Pooled demographics are presented in Table 2. On average AF-HFrEF patients were 4 years younger and had a higher proportion of males and prior MI than those with AF-HFpEF. AF-HFrEF patients typically had higher NYHA class (i.e. more symptomatic than AF-HFpEF). Mean ejection fraction ranged from 26-35% in AF-HFrEF and 51-63% in AF-HFpEF, with a variety of cut-off values for HFpEF, including 40%, 45%, 50% and 55%. Detailed characteristics by study, including a comparison of drug therapy, are presented in Supplementary Table B. Of particular note were the low rates of anticoagulation use (particularly in the cohort studies), despite indications for oral anticoagulation (mean $CHADS_2$ scores ranging from 2.0 to 3.3). Oral anticoagulant use was higher in those patients with AF-HFrEF compared to AF-HFpEF ($p<0.001$).

All-cause mortality

Ten studies were suitable for unadjusted meta-analysis of the primary outcome, totaling 45,100 patients.[8, 19, 21, 26-32] All-cause mortality was significantly higher in AF-HFrEF, with a pooled risk ratio of 1.24 compared to AF-HFpEF (95% CI 1.12-1.36, p<0.001; see Figure 2). In AF-HFrEF, all-cause mortality in 9 individual studies with long-term follow-up ranged from 13 to 55% and overall 24% of patients died (2088/8785).[8, 19, 21, 27-32] In AF-HFpEF, all-cause mortality in the 9 long-term studies ranged from 8 to 50% and overall 18% of patients died (1017/5758).

Sub-group analysis by study type confirmed higher mortality in AF-HFrEF compared to AF-HFpEF in both the post-hoc assessments of randomized trials as well as cohort studies (see Supplementary Figure A), with the difference in mortality greatest in the post-hoc randomized trials (interaction p=0.02). The relative increase in mortality for the AF-HFrEF group was unaffected by the average rate of anticoagulation (interaction p=0.83; see Supplementary Figure B) or by ejection fraction cut-off (interaction p=0.17; see Supplementary Figure C). In an exploratory meta-analysis, we also confirmed higher mortality in AF-HFrEF compared to AF-HFpEF regardless of whether the study population was predominantly heart failure (RR 1.24, 95% CI 1.04-1.49, p<0.001) or derived from patients with AF (RR 1.24, 95% CI 1.11-1.38, p=0.016), with an interaction p-value of 0.96. Results were unaffected by removal of the largest included study[26] (RR 1.23, 95% CI 1.09-1.39; p=0.001). There was no evidence of significant publication bias for the primary outcome (see Figure 3), although this cannot be excluded in light of the small number of trials and degree of heterogeneity.

Three studies provided adjusted HR for all-cause mortality comparing AF-HFrEF with AF-HFpEF, which were all consistent with the unadjusted meta-analysis results.[8, 28, 29] It was not appropriate to pool these results due to substantial differences in the adjustment variables

within each analysis (see Supplementary Table C). Of the studies not included in the meta-analysis, results from Pedersen *et al* were consistent with the overall results (long-term mortality greater in AF patients with an ejection fraction <35%).[35] McManus *et al* reported on a community cohort of heart failure patients and identified similar adjusted hazard ratios (HR) for pre-existing AF compared to sinus rhythm in HFrEF (1.15, 95% 1.05-1.26) and HFpEF (1.11, 95% CI 1.03-1.20).[34]

Incident stroke

Seven studies including 33,773 subjects were suitable for meta-analysis of incident stroke (see Figure 4A).[8, 19, 26, 28, 29, 31, 32] Of note, the follow-up period for stroke was short, with one study including in-hospital strokes only (mean duration of hospital admission 6.3 [range of 0-56] days)[28] and one study assessing 30-day readmission for ischemic stroke.[26] Two studies included fatal and non-fatal strokes.[8, 32] The rate of incident stroke was similar at 1.6% in AF-HFrEF (269/16967) and 1.3% in AF-HFpEF (213/16806). Meta-analysis revealed no significant difference between groups (RR 0.85, 95% CI 0.70-1.03, p=0.094).

One additional study not included in the meta-analysis discussed stroke as an outcome. McManus *et al* reported that pre-existing AF was associated with ischemic stroke only in those with HFpEF (adjusted HR compared to sinus rhythm 1.91, 95% CI 1.56-2.33; versus 1.07, 95% CI 0.82-1.39 in HFrEF).[34]

Heart failure hospitalization

Five studies including 31,583 patients were suitable for meta-analysis of heart failure hospitalization.[8, 26, 30-32] There was a numerical excess in those with AF-HFrEF, with 13.7% having one or more hospitalizations (2159/15779), compared to 7.9% in patients with AF-HFpEF (1256/15804). However this was not statistically significant on meta-analysis with

RR 1.21, 95% CI 0.96-1.53, p=0.115 (see Figure 4B).

Heart failure hospitalization was reported in two additional studies not included in the meta-analysis, both of which noted a non-significant but numerical excess in AF-HFrEF. Badheka *et al* reported an adjusted HR comparing AF-HFrEF with AF-HFpEF of 1.12 (95% CI 0.93-1.33, p=0.24)[29] and McManus *et al* reported an adjusted HR compared to sinus rhythm of 1.26 (95% CI 1.17-1.37) for AF-HFrEF and 1.16 (95% CI 1.05-1.27) for AF-HFpEF.[34]

Other outcomes

There were limited data available on other clinical outcomes. Parkash *et al* assessed in-hospital MI only (over 6.3 days) and found a lower rate in patients with AF-HFpEF (2.3% versus 7.3% with AF-HFrEF; p=0.012).[28] In Kotecha *et al*, there were very few incident MI events on longer term follow-up, numbering 47/3000 patients (1.6%) overall and no significant difference between AF-HFrEF and AF-HFpEF (p=0.16).[8] Rates of thromboembolism were reported in two studies, with no difference between groups: AF-HFrEF 19/691 (2.7%) for Banerjee *et al*[19] and 5/2736 (0.2%) for McMurray *et al*[31] compared to AF-HFpEF 17/585 (2.9%) and 8/3207 (0.2%) respectively. Badheka *et al* also documented no difference in progression of NYHA class between groups.[29] Three studies (n=7,941) reported on bleeding outcomes for AF-HFrEF versus AF-HFpEF, with no differences identified in the rate of bleeding.[19, 29, 31]

Discussion

In this systematic review and meta-analysis of over 54,000 patients, our principal finding was a significantly higher risk of death in AF patients with HFrEF compared to those with HFpEF. There was a crude mortality rate of 24% versus 18% respectively, over an average follow-up period of 2 years. Importantly, we identified no significant difference in incident stroke or heart failure hospitalization between the two groups. There was no consistent evidence of any difference in other cardiovascular or bleeding outcomes, however the use of anticoagulation was substantially below recommended levels.

Atrial fibrillation and heart failure commonly coexist.[11] Regardless of which condition arises first, patients suffer a substantial increase in cardiovascular and non-cardiovascular morbidity, as well as increased mortality, both in those with pre-existing and new-onset AF.[36, 37] Recent years have seen a focus on preventing strokes and thromboembolism in AF, with numerous large trials of novel oral anticoagulants. However, the principal causes of cardiovascular mortality in AF remain progressive heart failure and sudden death.[6] Heart failure can occur as a consequence of AF, secondary to the rapid pulse and morphological changes to atrial and ventricular structure and function (tachycardia-induced cardiomyopathy). Conversely, structural changes in chronic heart failure patients, with the addition of neurohormonal activation, make AF much more prevalent and can worsen ventricular function (tachycardia-accelerated cardiomyopathy). Furthermore, AF and heart failure may in some patients have a common cause (for example a genetic or acquired predisposition to cardiac dysfunction). As such, the two conditions are inter-connected and frequently seen in clinical practice.[3, 38]

Studies in heart failure have typically enrolled patients with left-ventricular systolic dysfunction, whereas outcomes in HFpEF have been less well documented. The latter, in

which impairment of diastolic relaxation leads to signs and symptoms of heart failure, is equal in prevalence or more common than HFrEF[16] and is associated with similar risk factors to those predicting mortality in AF patients.[39, 40] Hence defining clinical differences between the two types of heart failure is paramount, both for risk-stratification and patient management as well as healthcare policy generation. Comparative data on cardiovascular outcomes in patients with AF have been conflicting, resulting in a lack of focus on mortality as a preventable outcome in both AF-HFrEF and AF-HFpEF.

Our results showing excess mortality in AF-HFrEF are consistent with data for all heart failure patients, regardless of rhythm status. The Meta-analysis Global Group in Chronic Heart Failure (MAGGIC), performed an individual-patient meta-analysis of 41,972 subjects, with 79% in sinus rhythm.[41] Those with HFpEF were at a lower risk of death than HFrEF with a crude HR of 0.71, 95% CI 0.67-0.74 (the corresponding RR in our analysis was 0.81, 95% CI 0.73-0.89). We deliberately assessed data in unadjusted form, as the presence of interacting confounders in sub-group assessment cannot be controlled within a tabular meta-analysis. However there is little evidence of any modifying effect on risk, either in the MAGGIC analysis[41] or within the three studies that provided adjusted HR for direct comparison of AF-HFrEF with AF-HFpEF. There was a small but significant difference in age between the groups, however AF-HFpEF patients were older and adjustment would likely have exaggerated the divergence on mortality demonstrated. We did note a significant interaction according to study design, with data obtained from randomized studies showing higher death rates even with better medical therapy. Whilst this could represent a chance-effect, it could also be explained by selection biases within the randomized cohorts, particularly as patients were not randomized on the basis of their ejection fraction. No interactions were identified according to population, anticoagulation rate or ejection fraction

cut-off, suggesting that our finding of increased mortality in AF-HFrEF is consistent despite differences in study settings and methodology.

Medical therapy was surprisingly sub-optimal in the community cohorts with relatively poor uptake of ACE inhibitors and beta-blockers in AF-HFrEF patients compared to the randomized trials. This may reflect the view of clinicians on the benefit of these drugs in heart failure patients with AF, compared to the published data which predominantly relates to those in sinus rhythm. We have recently demonstrated that beta-blockers in HFrEF patients with AF do not reduce all-cause mortality, with an adjusted HR of 0·97 (95% CI 0·83-1·14) versus placebo, compared to 0·73 (95% CI 0·67-0·80) in those with sinus rhythm (interaction p=0.002).[8] We also identified no significant reduction in cardiovascular and heart failure related hospitalization in AF-HFrEF patients given beta-blockers, highlighting the importance of obtaining AF-specific data, rather than extrapolation from other populations.

Regardless of study design, the use of anticoagulation was noticeably discordant with current guidelines.[42, 43] Only 55% in the AF-HFrEF group and 50% with AF-HFpEF were on oral anticoagulation despite having risk factors for stroke that should lead to initiation of therapy. Strokes in patients with AF are associated with larger neurological deficits, longer hospital stays, lower discharge rates to home and higher mortality.[44] We did not identify any significant difference in incident stroke between AF-HFrEF and AF-HFpEF, consistent with recently published data.[45] As such, both groups of patients should receive adequate anticoagulation, with vitamin K antagonists (VKA) or non-VKA oral anticoagulants, in order to attain low rates of residual adverse events.[46] With regards to risk assessment using the CHA_2DS_2-VASc score[1], our data confirm that the presence of heart failure is important, regardless of ejection fraction.[47]

Limitations

This review is based on tabular reported results of independent studies prepared according to explicit, reproducible methodology[22] of published and unpublished data. The main limiting factor in these analyses were the component studies, which by their nature were observational cohorts, either post-hoc examinations of randomized trials or cohort studies. Patients with AF-HFrEF/AF-HFpEF constituted 30% of the total population studied and therefore selection biases should be considered. Owing to the expected differences in study design and populations, we pre-specified a random-effects model, with additional fixed-effect sensitivity analyses of the primary outcome and relevant sub-groups. Substantial heterogeneity was noted for all-cause mortality, although this was rendered non-significant by stratification according to study design. There were insufficient data to perform meta-regression on baseline variables such as age and gender. Publication bias was not identified, although funnel plot symmetry and associated statistical measurements can be misleading, particularly in cases where heterogeneity is high.[48] The methodological quality of the included studies was variable and the incident stroke rate was low, although this likely reflects the short follow-up periods for this particular outcome. Very few studies recorded the type of AF (paroxysmal/persistent/permanent) and there was inconsistency in the ejection fraction cut-off for HFpEF. Future studies would be improved by using a standardized criterion (for example >50% as suggested by heart failure guidelines[16, 49]) and ensuring that patients with AF are adequately anticoagulated.

Conclusion

Patients with atrial fibrillation and heart failure have substantial morbidity regardless of left-ventricular ejection fraction. Systematic review of over 54,000 patients demonstrates higher rates of all-cause mortality in those with reduced ejection fraction but similar stroke risk and heart failure hospitalization compared to patients with preserved left-ventricular function. Further attention is warranted to refocus on mortality as a preventable outcome, to standardize the diagnosis of preserved ejection fraction and to improve the rate of anticoagulation in all AF patients with heart failure.

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Author contributions:

DK contributed to the study concept and data extraction, performed the statistical analysis and drafting of the manuscript. RC developed the eligibility criteria, performed the primary literature search and contributed to data extraction and drafting of the manuscript. DAL contributed to the conception of the study, data extraction and critical revision of the manuscript. PK provided critical revision of the manuscript for intellectual content. GYHL contributed to the conception of the study, data interpretation and critical revision of the manuscript for intellectual content.

Competing interests:

All authors have completed the ICMJE uniform disclosure form (www.icmje.org/coi_disclosure.pdf) and declare the following, all outside of the submitted work: DK is the lead for the Beta-blockers in Heart Failure Collaborative Group (BB-meta-HF) and the RAte control Therapy Evaluation in Atrial Fibrillation (RATE-AF) trial, and has received honoraria and research grants from Menarini and professional development support from Daiichi-Sankyo; RC has no relevant conflicts; DAL has received educational grants from Bayer Healthcare and Boehringer Ingelheim and served as a speaker for Boehringer Ingelheim, Bayer Healthcare and BMS/Pfizer; PK has received consulting fees and honoraria from MEDA Pharma, AstraZeneca, Bayer Healthcare, Biosense Webster, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi-Sankyo, Medtronic, Merck, Pfizer, Sanofi and Servier and received research grants from MEDA Pharma, Bristol-Myers Squibb, Medtronic, Sanofi and St. Jude Medical; GYHL has served as a consultant for Bayer, Astellas, Merck, Sanofi, Bristol-Myers Squibb/Pfizer, Daiichi-Sankyo, Biotronik, Portola and Boehringer

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None required.

Transparency declaration:

DK affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned and registered have been explained.

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Table 1: Description of studies

Study	Design	Sample size	Follow-up period	HFpEF definition
Badheka, 2011 [29]	Post-hoc analysis of AF patients randomized to rate versus rhythm-control (AFFIRM trial)	722 with HF and documented LVEF, from a total population of 4060	Mean 3.4 years	≥ 50%
Banerjee, 2012 [19]	Retrospective cohort study of patients diagnosed with AF at a single French cardiology unit	1276 with non-valvular AF and LVEF available, from a total population of 7156	Mean 1.3 years	≥ 50%
Eapen, 2013* [26]	Retrospective cohort study of patients admitted with decompensated HF (ADHERE-Core Medicare registry)	30557 with AF and LVEF recorded, from a total population of 80416	30 days	≥ 40%
Fung, 2007 [33]	Prospective cohort study of patients admitted with HF	72 with AF, from a total population of 238	Median 0.88 years	≥ 50%
Kotecha, 2014 [8]	Post-hoc analysis of HF patients randomized to beta-blockers or placebo pooled from 10 trials (BB-meta-HF)	3050 with AF and LVEF recorded, from a population of 18254	Mean 1.5 years	≥ 45%
Linssen, 2011 [30]	Post-hoc analysis of HF patients randomized to different levels of counselling and support	336 with AF and interpretable echocardiograms, from a total population of 1023	1.5 years	≥ 40%
McManus, 2013 [34]	Retrospective cohort study of heart failure patients from 4 centers in US	9081 with pre-existing AF, from a total population of 23,644	Median 1.8 years	≥ 50%
McMurray, 2013 [31]	Post-hoc analysis of AF patients randomized to a novel oral anticoagulant or warfarin (ARISTOTLE trial)	5943 with AF and either HFrEF or HFpEF, from a total population of 18201	Median 1.5 years	> 40%
Olsson, 2006 [32]	Post-hoc analysis of HF patients randomized in 3 studies to an angiotensin receptor blocker or placebo (CHARM trials)	1148 with AF, from a total population of 7601	Median 3.1 years	> 40%
Pai, 2007 [27]	Retrospective cohort study of patients undergoing echocardiography at a single US center	1168 with AF, from a total population of 8,931	Mean 2.6 years	≥ 55%
Parkash, 2005 [28]	Retrospective cohort study of patients attending a single US emergency department with HF and AF	478 with an echocardiogram within 1 month, from a total population of 1749	Mean 3.3 years	> 50%
Pedersen, 2005 [35]	Prospective cohort study of patients admitted to 27 Danish centers with an acute myocardial infarction	332 with AF/atrial flutter, HF history and LVEF from a total population of 6676	5 years	> 50%
Shamagian, 2006 [21]	Retrospective cohort study of patients admitted for HF at a single Spanish cardiology unit	424 with AF and measured LVEF, from a total population of 1636	Mean 3.1 years	≥ 50%

AF, atrial fibrillation; HF, heart failure; LVEF, left-ventricular ejection fraction; AFFIRM, Atrial Fibrillation Follow-Up Investigation of Rhythm Management; ADHERE, Acute Decompensated Heart Failure National Registry; BB-meta-HF, Beta-blockers in Heart Failure Collaborative Group; ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; CHARM, Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity. * E-published 2013; in-print 2014.

Table 2: Pooled weighted characteristics

Characteristic	AF-HFrEF	AF-HFpEF
Age, mean (SD)	74.6 years	78.5 years
Male, %	67.7%	41.1%
Prior myocardial infarction, %	38.3%	22.5%
Diabetes, %	32.0%	32.7%
LVEF, mean %	30.7%	56.4%
Oral anticoagulant use, %	54.8%	49.9%

Pooled results for 10 studies (where data available), weighted according to sample size.

Supplementary Table A: Risk of bias assessment

Study	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcome	Incomplete outcome data	Selective reporting
Badheka, 2011	Low risk	Low risk	Low risk	Unclear	High risk	Low risk
Banerjee, 2012	Low risk	Low risk	Low risk	Unclear	High risk	Low risk
Eapen, 2013	Low risk	Low risk	Low risk	Low risk	High risk	Low risk
Fung, 2007	Low risk	Unclear	Low risk	Unclear	Unclear	Low risk
Kotecha, 2014	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Linssen, 2011	Low risk	Low risk	Low risk	Low risk	High risk	Low risk
McManus, 2013	Low risk	Low risk	Low risk	Unclear	High risk	Low risk
McMurray, 2013	Low risk	Low risk	Low risk	Low risk	High risk	Low risk
Olsson, 2006	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Pai, 2007	Low risk	Unclear	Low risk	Unclear	Unclear	Unclear
Parkash, 2005	Low risk	Low risk	Low risk	Unclear	High risk	Low risk
Pedersen, 2004	Low risk	Unclear	Low risk	Low risk	High risk	Low risk
Shamagian, 2005	Low risk	Low risk	Low risk	Unclear	High risk	Unclear

Risk of bias reported for each domain using the Risk of Bias Assessment Tool for Non-randomized Studies (RoBANS).[23] High risk in the incomplete outcome data category is attributed to the inherent selection biases of assessing patients with an available measurement of ejection fraction.

Supplementary Table B: Detailed characteristics of studies

Study	Age, years (SD)	Male	Diabetes	Prior MI	NYHA Class	Mean ejection fraction (SD)	Oral anticoagulant	ACEi/ARB	Beta-blocker	Digoxin	Mean $CHADS_2$ score (SD)
Badheka, 2011	rEF 68 (9) pEF 71 (8)	rEF 74% pEF 49%	rEF 29% pEF 28%	rEF 40% pEF 21%	Class >1: rEF 38% pEF 24%	n/s	rEF 90% pEF 89%	rEF 77% pEF 51%	rEF 37% pEF 44%	rEF 76% pEF 64%	rEF 2.5 (1.1) pEF 2.8 (1.1)
Banerjee, 2012	rEF 71 (12) pEF 75 (13)	rEF 77% pEF 50%	rEF 24% pEF 26%	rEF 50% pEF 31%	n/s	rEF 33% (9) pEF 60% (7)	rEF 60% pEF 61%	rEF 57% pEF 38%	rEF 50% pEF 50%	rEF 31% pEF 27%	rEF 2.2 (1.0) pEF 2.6 (1.1)
Eapen, 2013 [a]	rEF 79 (7) pEF 81 (7)	rEF 61% pEF 37%	rEF 36% pEF 35%	rEF 39% pEF 23%	n/s	n/s	rEF 49% pEF 47%	rEF 64% pEF 54%	rEF 62% pEF 55%	n/s	rEF 3.1 (1.2) pEF 3.3 (1.1)
Fung, 2007	rEF 63 (7) pEF 74 (9)	rEF 63% pEF 21%	rEF 20% pEF 21%	n/s	Mean: rEF 2.76 (0.44) pEF 2.61 (0.51)	rEF 29% (6) pEF 63% (9)	n/s	rEF 80% pEF 14%	rEF 70% pEF 21%	rEF 77% pEF 71%	n/s
Kotecha, 2014 [b]	rEF 67 (10) pEF 77 (5)	rEF 82% pEF 47%	rEF 23% pEF 23%	rEF 40% pEF 25%	rEF II 23%, III 65%, IV 8% pEF II 56%, III 38%, IV 4%	rEF 27% (7) pEF 54% (8)	rEF 59% pEF 36%	rEF 95% pEF 89%	randomized	rEF 84% pEF 75%	rEF 2.0 (1.0) pEF 2.6 (0.8)
Linssen, 2011	rEF 71 (10) pEF 75 (9)	rEF 70% pEF 57%	rEF 25% pEF 26%	rEF 40% pEF 22%	rEF II 47%, III 50%, IV 3% pEF II 53%, III 42%, IV 5%	rEF 26% (8) pEF 51% (9)	rEF 93% pEF 86%	rEF 88% pEF 78%	rEF 69% pEF 55%	rEF 59% pEF 50%	n/s
McManus, 2013 [c]	78 (10)	52%	24%	11%	n/s	n/s	50%	56%	66%	30%	n/s
McMurray, 2013 [d]	rEF 68 (14) pEF 69 (14)	rEF 79% pEF 58%	rEF 27% pEF 25%	rEF 28% pEF 18%	rEF II 50%, III 22%, IV 1% pEF II 62%, III 21%, IV 1%	rEF 35% (9) pEF 56% (12)	rEF 61% pEF 51%	rEF 81% pEF 77%	rEF 75% pEF 69%	rEF 47% pEF 39%	rEF 2.2 (1.2) pEF 2.7 (1.1)
Olsson, 2006	rEF 68 (10) pEF 71 (10)	rEF 78% pEF 58%	rEF 27% pEF 23%	rEF 44% pEF 24%	rEF II 29%, III 66%, IV 6% pEF II 56%, III 41% IV 3%	rEF 29% (8) pEF 55% (9)	rEF 77% pEF 73%	ARB randomized	rEF 50% pEF 45%	rEF 80% pEF 66%	n/s
Pai, 2007 [c,e]	72 (10)	97%	n/s	n/s	n/s	47% (17)	n/s	n/s	n/s	n/s	n/s
Parkash, 2005 [a]	rEF 72 (13) pEF 76 (12)	rEF 65% pEF 38%	rEF 30% pEF 26%	rEF 43% pEF 20%	n/s	rEF 33% (9) pEF 58% (7)	rEF 77% pEF 78%	rEF 70% pEF 43%	rEF 58% pEF 59%	rEF 58% pEF 46%	n/s
Pedersen, 2005 [b,c]	75	62%	15%	27%	n/s	33%	n/s	n/s	n/s	n/s	n/s
Shamagian, 2006	rEF 68 (11) pEF 72 (9)	rEF 71% pEF 46%	rEF 21% pEF 20%	rEF 39% pEF 23%	Class III/IV: rEF 77% pEF 74%	n/s	rEF 53% pEF 59%	rEF 68% pEF 49%	rEF 25% pEF 17%	rEF 66% pEF 46%	n/a

SD, standard deviation; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; rEF, reduced ejection fraction; pEF, preserved ejection fraction; n/s, not specified. [a] Medication rates are those at time of discharge. [b] Includes patients with AF and atrial flutter. [c] rEF and pEF groups combined. [d] rEF group includes asymptomatic patients; values are median (interquartile range). [e] Symptom status unknown; quoted figures are for the whole AF population.

Supplementary Table C: Adjusted comparative hazard ratios for all-cause mortality

Study	Ejection fraction cut-off	Adjusted hazard ratio for all-cause mortality: AF-HFrEF versus AF-HFpEF		
		Point estimate	95% CI	Adjustment variables
Badheka, 2011	≥ 50%	1.61	1.18-2.17	Age, gender, rhythm at randomization, duration of AF, diabetes, hypertension, CAD, stroke, mitral regurgitation, smoking, NYHA class, ACEi, beta-blockers, CCB, digoxin, randomization arm
Kotecha, 2014	≥ 45%	1.33	0.83-2.12	Age, gender, diabetes, previous MI, prior coronary revascularization, hypertension, heart rate, ACEi/ARB, digoxin, diuretic therapy, oral anticoagulation, randomization arm (study stratified)
Parkash, 2005	>50%	1.09	0.80-1.48	Age, gender, renal insufficiency, diabetes, hypertension, CAD, COPD, stroke, history of cancer, comorbid illnesses at the time of hospitalization including acute MI, infection, respiratory failure or pulmonary embolism, smoking, serum sodium, heart rate, ACEi, ARB, beta-blockers, aspirin, warfarin, digoxin, antiarrhythmic drugs, statins at discharge

CAD, coronary artery disease; CCB, calcium channel blocker; COPD, chronic obstructive pulmonary disease.

Figure Legends

Figure 1: Study selection diagram

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Figure 2: Meta-analysis of all-cause mortality

Meta-analysis for the primary outcome, with the diamond and dotted line representing the pooled difference using a random-effects model. I^2 is the percentage of total variation across studies due to heterogeneity (p for heterogeneity=0.002).

Figure 3: Assessment of publication bias for all-cause mortality

Funnel plot diagram for primary outcome demonstrating relative symmetry with no observable small-study effects (Begg's p=0.47, Egger's p=0.73).

Figure 4: Meta-analysis of incident stroke and heart failure-related hospitalization

Random-effects model meta-analysis. Incident stroke heterogeneity p=0.40. Heart failure hospitalization heterogeneity p<0.001.

Supplementary Figure A: Meta-analysis according to study design

Fixed-effects model meta-analysis. Interaction for study design p=0.02. Post-hoc randomized controlled trial (RCT) group heterogeneity p=0.103. Cohort study group heterogeneity p=0.111. Overall heterogeneity p=0.002.

Supplementary Figure B: Meta-analysis according to anticoagulation use

Random-effects model meta-analysis. Rate of anticoagulation interaction p=0.83. >70% group heterogeneity p=0.002. ≤70% group heterogeneity p=0.019. Overall heterogeneity p=0.002.

Supplementary Figure C: Meta-analysis according to HFpEF cut-off

Random-effects model meta-analysis. HFpEF definition interaction p=0.17. Left-ventricular ejection fraction (LVEF) ≥50% group heterogeneity p=0.10. <50% definition group heterogeneity p=0.008. Overall heterogeneity p=0.002.

Figure 1

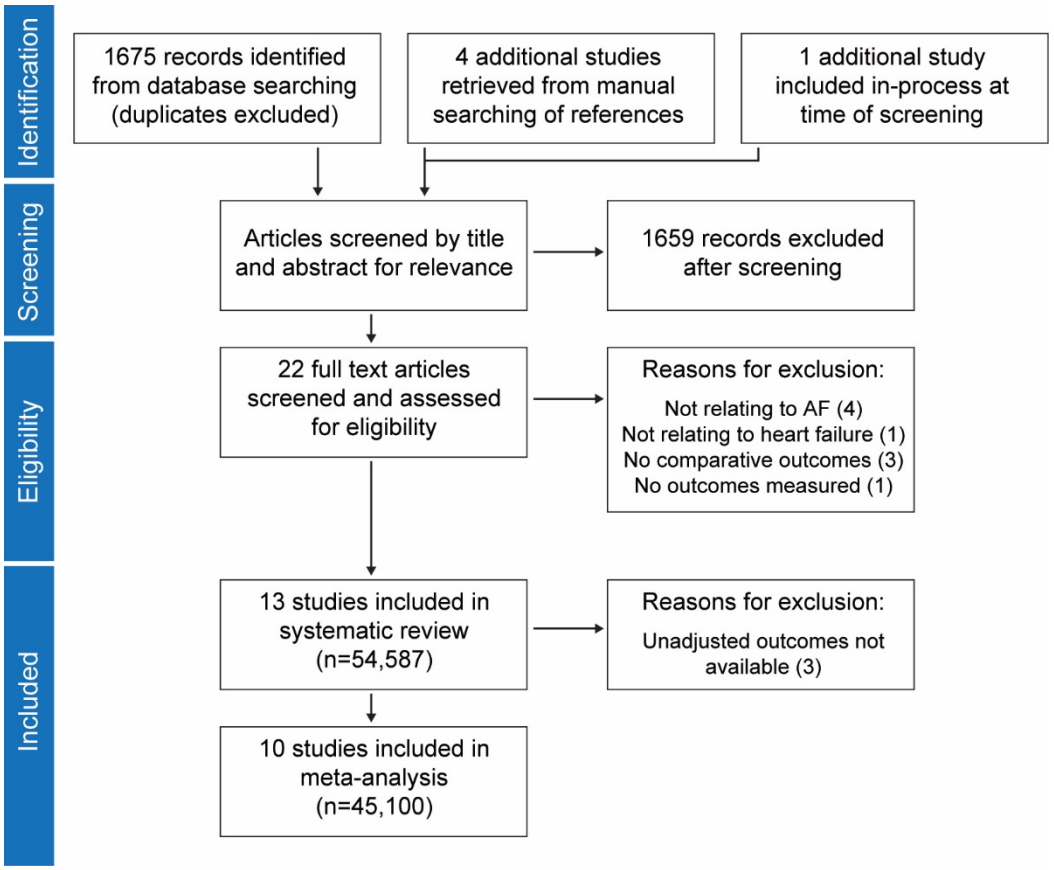

Identification
Screening
Eligibility
Included
1675 records identified from database searching (duplicates excluded)
4 additional studies retrieved from manual searching of references
1 additional study included in-process at time of screening
Articles screened by title and abstract for relevance
1659 records excluded after screening
22 full text articles screened and assessed for eligibility
Reasons for exclusion:
Not relating to AF (4)
Not relating to heart failure (1)
No comparative outcomes (3)
No outcomes measured (1)
13 studies included in systematic review (n=54,587)
Reasons for exclusion:
Unadjusted outcomes not available (3)
10 studies included in meta-analysis (n=45,100)

Figure 2

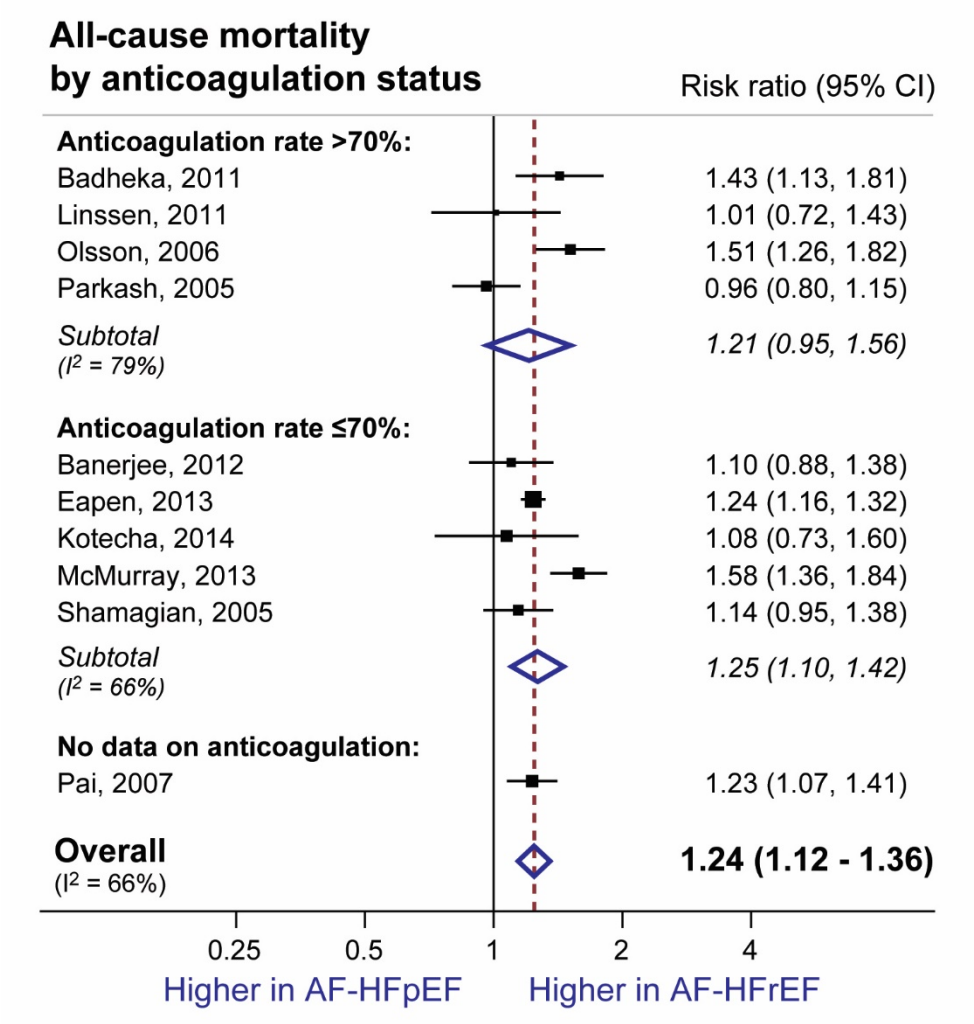

All-cause mortality
by anticoagulation status
Risk ratio (95% CI)
Anticoagulation rate >70%:
Badheka, 2011
1.43 (1.13, 1.81)
Linssen, 2011
1.01 (0.72, 1.43)
Olsson, 2006
1.51 (1.26, 1.82)
Parkash, 2005
0.96 (0.80, 1.15)
Subtotal
(I² = 79%)
1.21 (0.95, 1.56)
Anticoagulation rate ≤70%:
Banerjee, 2012
1.10 (0.88, 1.38)
Eapen, 2013
1.24 (1.16, 1.32)
Kotecha, 2014
1.08 (0.73, 1.60)
McMurray, 2013
1.58 (1.36, 1.84)
Shamagian, 2005
1.14 (0.95, 1.38)
Subtotal
(I² = 66%)
1.25 (1.10, 1.42)
No data on anticoagulation:
Pai, 2007
1.23 (1.07, 1.41)
Overall
(I² = 66%)
1.24 (1.12 - 1.36)
0.25
0.5
1
2
4
Higher in AF-HFpEF
Higher in AF-HFrEF

Figure 3

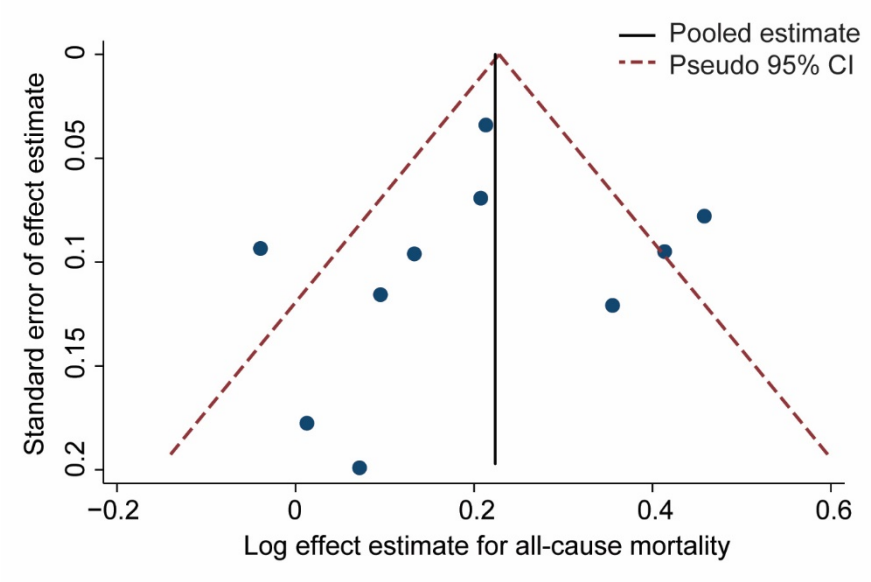
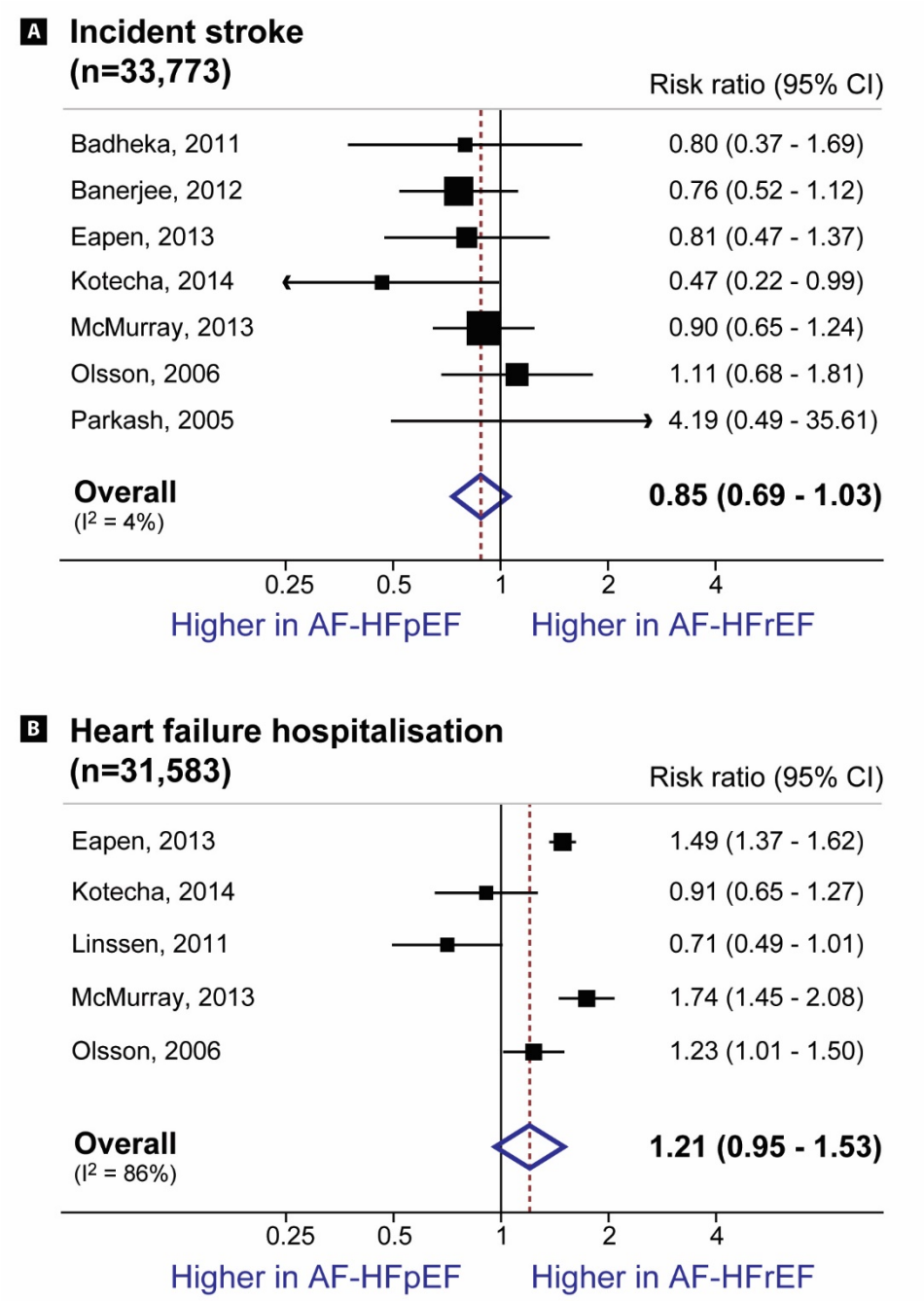
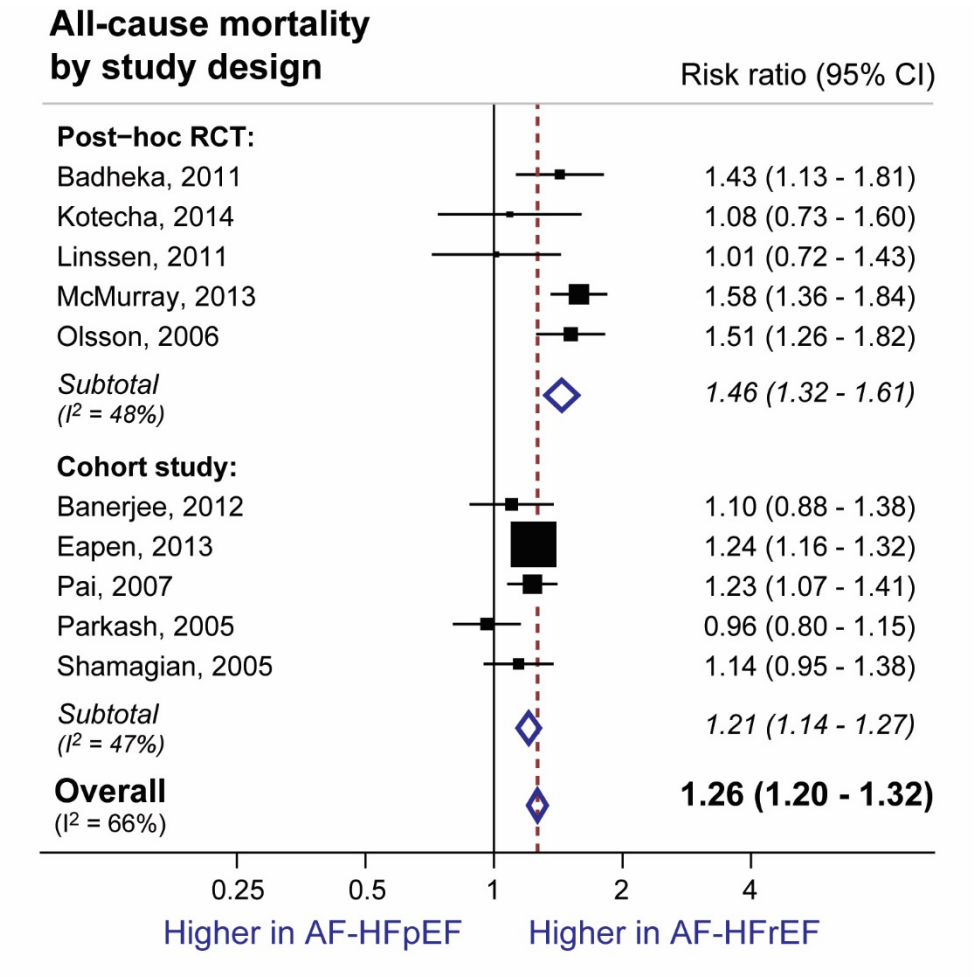

Pooled estimate
Pseudo 95% CI
Standard error of effect estimate
0
0.05
0.1
0.15
0.2
−0.2
0
0.2
0.4
0.6
Log effect estimate for all-cause mortality

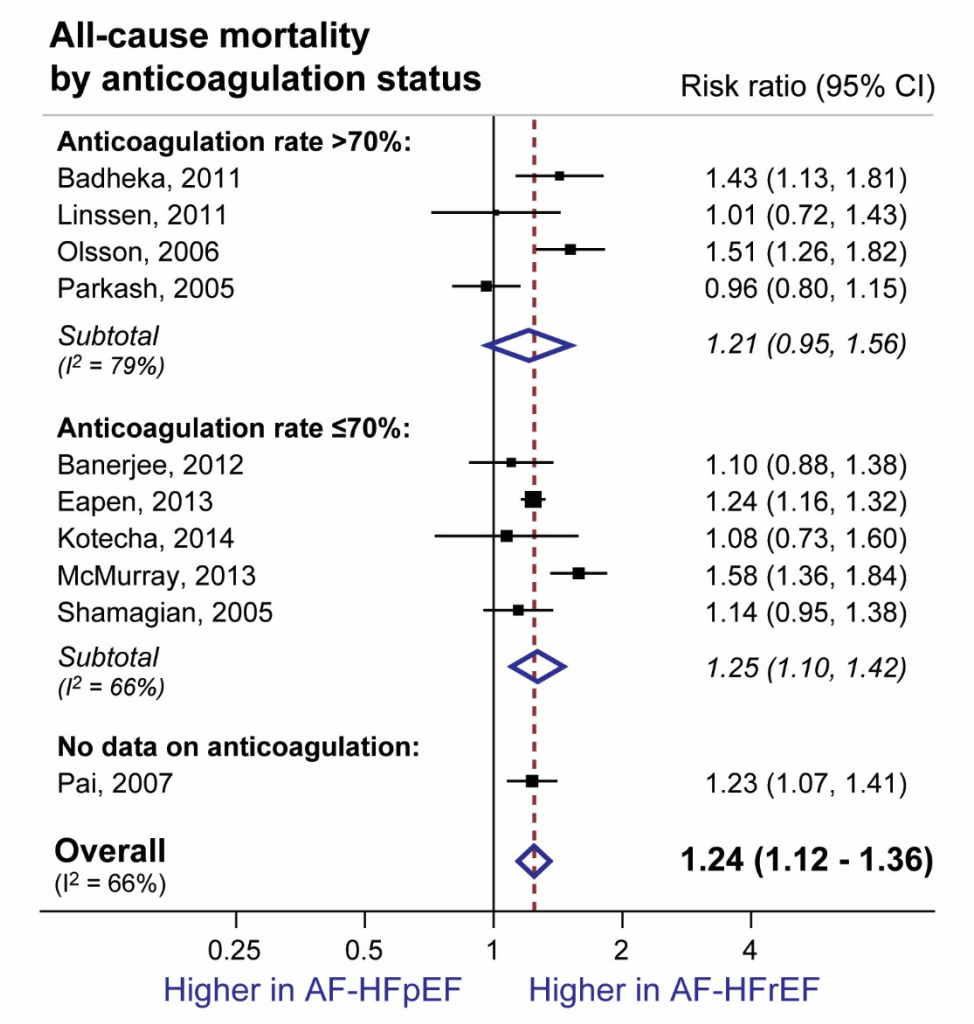
Figure 4


A
Incident stroke
(n=33,773)
Risk ratio (95% CI)
Badheka, 2011
0.80 (0.37 - 1.69)
Banerjee, 2012
0.76 (0.52 - 1.12)
Eapen, 2013
0.81 (0.47 - 1.37)
Kotecha, 2014
0.47 (0.22 - 0.99)
McMurray, 2013
0.90 (0.65 - 1.24)
Olsson, 2006
1.11 (0.68 - 1.81)
Parkash, 2005
4.19 (0.49 - 35.61)
Overall
(I2 = 4%)
0.85 (0.69 - 1.03)
0.25
0.5
1
2
4
Higher in AF-HFpEF
Higher in AF-HFrEF
B
Heart failure hospitalisation
(n=31,583)
Risk ratio (95% CI)
Eapen, 2013
1.49 (1.37 - 1.62)
Kotecha, 2014
0.91 (0.65 - 1.27)
Linssen, 2011
0.71 (0.49 - 1.01)
McMurray, 2013
1.74 (1.45 - 2.08)
Olsson, 2006
1.23 (1.01 - 1.50)
Overall
(I2 = 86%)
1.21 (0.95 - 1.53)
0.25
0.5
1
2
4
Higher in AF-HFpEF
Higher in AF-HFrEF

Supplementary Figure A



Supplementary Figure B



Supplementary Figure C